Clinical trial results:
A first-in-human, two-part (open label, and randomized/double blind/placebo controlled), single- and repeat-dose study of CSJ137 in erythropoietin-treated chronic hemodialysis patients with functional iron-deficiency anemia

Summary

EudraCT number	2017-002926-19
Trial protocol	GB
Global end of trial date	13 May 2020

Results information

Result version number	v1
This version publication date	12 April 2021
First version publication date	12 April 2021

Trial information

Trial identification

Sponsor protocol code	CCSJ137X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02570854
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to:
- To assess safety and tolerability following a single dose of CSJ137
- To determine the minimum pharmacologically active dose (PAD) of CSJ137

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, were recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Evidence for comparator: -

Actual start date of recruitment	22 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	40
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenteric study in which 40 participants were enrolled in 10 centers across 2 countries: Israel (6) and USA (4).

Pre-assignment

Screening details:

All the participants were assigned to one of the 8 open label dose cohorts.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding occurred in the Part 1 of this study as it was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Dose 1

Arm description:

participants received a single dose of CSJ137 having lower ferritin inclusion criteria than participants in subsequent cohorts

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

participants received a single dose of CSJ137 having lower ferritin inclusion criteria than participants in subsequent cohorts

Arm title	Cohort 1: Dose 1a

Arm description:

one participant had a dosing error and was thus reported in a separate group. Dose 1a was in the range between Dose 6 and Dose 7. The participant had lower ferritin inclusion criteria than participants in subsequent cohorts

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

one participant had a dosing error and was thus reported in a separate group. Dose 1a was in the range between Dose 6 and Dose 7. The participant had lower ferritin inclusion criteria than participants in subsequent cohorts

Arm title	Cohort 2: Dose 2

Arm description:

participants received the same dose level as participants in Cohort 1: Dose 1 group, but had higher ferritin inclusion criteria than participants from Cohort 1

Arm type	Experimental

Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

participants received the same dose level as participants in Cohort 1: Dose 1 group, but had higher ferritin inclusion criteria than participants from Cohort 1

Arm title	Cohort 3: Dose 3

Arm description:

single dose of CSJ137

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

participants received a single dose of CSJ137

Arm title	Cohort 4: Dose 4

Arm description:

single dose of CSJ137

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

participants received a single dose of CSJ137

Arm title	Cohort 5: Dose 5

Arm description:

single dose of CSJ137

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

participants received a single dose of CSJ137

Arm title	Cohort 6: Dose 6

Arm description:

single dose of CSJ137

Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: participants received a single dose of CSJ137

Arm title	Cohort 7: Dose 7
Arm description: single dose of CSJ137	
Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: participants received a single dose of CSJ137	

Arm title	Cohort 8: Dose 8
Arm description: single dose of CSJ137	
Arm type	Experimental
Investigational medicinal product name	CSJ137
Investigational medicinal product code	CSJ137
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: participants received a single dose of CSJ137	

Number of subjects in period 1	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2
Started	5	1	5
Pharmacodynamics (PD) analysis set	5	1	5
Completed	4	1	5
Not completed	1	0	0
Subject/guardian decision	1	-	-

Number of subjects in period 1	Cohort 3: Dose 3	Cohort 4: Dose 4	Cohort 5: Dose 5
Started	3	6	3
Pharmacodynamics (PD) analysis set	3	6	3
Completed	3	6	3
Not completed	0	0	0
Subject/guardian decision	-	-	-

Number of subjects in period 1	Cohort 6: Dose 6	Cohort 7: Dose 7	Cohort 8: Dose 8
Started	6	5	6

Pharmacodynamics (PD) analysis set	6	5	6
Completed	6	5	6
Not completed	0	0	0
Subject/guardian decision	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Dose 1
Reporting group description:	
participants received a single dose of CSJ137 having lower ferritin inclusion criteria than participants in subsequent cohorts	
Reporting group title	Cohort 1: Dose 1a
Reporting group description:	
one participant had a dosing error and was thus reported in a separate group. Dose 1a was in the range between Dose 6 and Dose 7. The participant had lower ferritin inclusion criteria than participants in subsequent cohorts	
Reporting group title	Cohort 2: Dose 2
Reporting group description:	
participants received the same dose level as participants in Cohort 1: Dose 1 group, but had higher ferritin inclusion criteria than participants from Cohort 1	
Reporting group title	Cohort 3: Dose 3
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 4: Dose 4
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 5: Dose 5
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 6: Dose 6
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 7: Dose 7
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 8: Dose 8
Reporting group description:	
single dose of CSJ137	

Reporting group values	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2
Number of subjects	5	1	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	1	3
From 65-84 years	1	0	2
85 years and over	0	0	0

Age Continuous			
Units: Years			
arithmetic mean	58.20	61.00	48.20
standard deviation	± 8.319	± 999	± 22.231
Sex: Female, Male			
Units: Participants			
Female	4	0	2
Male	1	1	3
Race/Ethnicity, Customized			
Units: Subjects			
Other	5	1	5
Hispanic/Latino	0	0	0

Reporting group values	Cohort 3: Dose 3	Cohort 4: Dose 4	Cohort 5: Dose 5
Number of subjects	3	6	3
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	3	2
From 65-84 years	0	3	1
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	56.67	62.33	60.00
standard deviation	± 9.452	± 11.742	± 6.557
Sex: Female, Male			
Units: Participants			
Female	0	2	1
Male	3	4	2
Race/Ethnicity, Customized			
Units: Subjects			
Other	3	6	3
Hispanic/Latino	0	0	0

Reporting group values	Cohort 6: Dose 6	Cohort 7: Dose 7	Cohort 8: Dose 8
Number of subjects	6	5	6
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	5	5	1
From 65-84 years	1	0	5
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	59.83	52.20	67.17
standard deviation	± 13.212	± 10.663	± 16.654
Sex: Female, Male			
Units: Participants			
Female	5	3	1
Male	1	2	5
Race/Ethnicity, Customized			
Units: Subjects			
Other	5	5	6
Hispanic/Latino	1	0	0

Reporting group values	Total		
Number of subjects	40		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	27		
From 65-84 years	13		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	18		
Male	22		
Race/Ethnicity, Customized			
Units: Subjects			
Other	39		
Hispanic/Latino	1		

End points

End points reporting groups

Reporting group title	Cohort 1: Dose 1
Reporting group description: participants received a single dose of CSJ137 having lower ferritin inclusion criteria than participants in subsequent cohorts	
Reporting group title	Cohort 1: Dose 1a
Reporting group description: one participant had a dosing error and was thus reported in a separate group. Dose 1a was in the range between Dose 6 and Dose 7. The participant had lower ferritin inclusion criteria than participants in subsequent cohorts	
Reporting group title	Cohort 2: Dose 2
Reporting group description: participants received the same dose level as participants in Cohort 1: Dose 1 group, but had higher ferritin inclusion criteria than participants from Cohort 1	
Reporting group title	Cohort 3: Dose 3
Reporting group description: single dose of CSJ137	
Reporting group title	Cohort 4: Dose 4
Reporting group description: single dose of CSJ137	
Reporting group title	Cohort 5: Dose 5
Reporting group description: single dose of CSJ137	
Reporting group title	Cohort 6: Dose 6
Reporting group description: single dose of CSJ137	
Reporting group title	Cohort 7: Dose 7
Reporting group description: single dose of CSJ137	
Reporting group title	Cohort 8: Dose 8
Reporting group description: single dose of CSJ137	

Primary: Number of participants with adverse events and serious adverse events

End point title	Number of participants with adverse events and serious adverse events[1]
End point description: Adverse events were collected from first dose of study treatment until end of study treatment Day 85. Any sign or symptom that occurred during the study treatment were collected.	
End point type	Primary
End point timeframe: Day 1 to Day 85 (end of study)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

End point values	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2	Cohort 3: Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	1	5	3
Units: Participants				
Patients with AEs	5	1	4	3
Serious AEs	3	0	2	3

End point values	Cohort 4: Dose 4	Cohort 5: Dose 5	Cohort 6: Dose 6	Cohort 7: Dose 7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	6	5
Units: Participants				
Patients with AEs	5	2	3	2
Serious AEs	0	0	1	0

End point values	Cohort 8: Dose 8			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants				
Patients with AEs	3			
Serious AEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Hemoglobin (Hgb) response

End point title	Number of participants with Hemoglobin (Hgb) response[2]

End point description:

The Hgb response was determined by levels of hemoglobin in blood, without the subject showing evidence of liver dysfunction or other safety concerns.

End point type	Primary

End point timeframe:

Day 29

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this outcome

End point values	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2	Cohort 3: Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	1	5	3
Units: Participants				
Hgb response	0	0	2	1

End point values	Cohort 4: Dose 4	Cohort 5: Dose 5	Cohort 6: Dose 6	Cohort 7: Dose 7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	6	4
Units: Participants				
Hgb response	2	1	1	0

End point values	Cohort 8: Dose 8			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants				
Hgb response	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak concentration (Cmax) of CSJ137 in serum

End point title	Peak concentration (Cmax) of CSJ137 in serum

End point description:

Cmax is the observed maximum plasma (or serum or blood) concentration following administration (ug/mL)

End point type	Secondary

End point timeframe:

pre-dose, 0.5 hours and 6 hours post-dose on Day 1, 2, 3, 5, 12, 19, 28, and 84

End point values	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2	Cohort 3: Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	1	5	3
Units: ug/mL				
arithmetic mean (standard deviation)	0.232 (± 0.193)	40.7 (± 999)	0.235 (± 0.0585)	1.49 (± 1.20)

End point values	Cohort 4: Dose 4	Cohort 5: Dose 5	Cohort 6: Dose 6	Cohort 7: Dose 7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	6	5
Units: ug/mL				
arithmetic mean (standard deviation)	1.88 (± 2.09)	4.38 (± 4.02)	17.1 (± 3.06)	65.7 (± 15.7)

End point values	Cohort 8: Dose 8			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ug/mL				
arithmetic mean (standard deviation)	197 (± 37.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of CSJ137 serum concentration and calculation of AUClast

End point title	Measurement of CSJ137 serum concentration and calculation of AUClast

End point description:

AUClast is the area under the curve calculated to the last quantifiable concentration point (day*ug/mL)

End point type	Secondary

End point timeframe:

pre-dose, 0.5 hours and 6 hours post-dose on Day 1, 2, 3, 5, 12, 19, 28, and 84

End point values	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2	Cohort 3: Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	1	5	3
Units: day*ug/mL				
arithmetic mean (standard deviation)	1.11 (± 1.14)	449 (± 999)	0.893 (± 0.254)	9.19 (± 9.87)

End point values	Cohort 4: Dose 4	Cohort 5: Dose 5	Cohort 6: Dose 6	Cohort 7: Dose 7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	6	5

Units: day*ug/mL				
arithmetic mean (standard deviation)	11.1 (± 15.0)	34.7 (± 37.3)	269 (± 72.8)	799 (± 145)

End point values	Cohort 8: Dose 8			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: day*ug/mL				
arithmetic mean (standard deviation)	3030 (± 839)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment Day 85 plus 30 days post treatment (Day 115).

Adverse event reporting additional description:

Any sign or symptom collected from first dose of study treatment until end of study treatment Day 85 plus 30 days post treatment (Day 115).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Cohort 1: Dose 1
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 1: Dose 1a
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 2: Dose 2
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 3: Dose 3
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 4: Dose 4
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 5: Dose 5
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 6: Dose 6
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 7: Dose 7
Reporting group description:	
single dose of CSJ137	
Reporting group title	Cohort 8: Dose 8
Reporting group description:	
single dose of CSJ137	
Reporting group title	Total
Reporting group description:	
Total	

Serious adverse events	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Myoclonus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Subcapsular renal haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3: Dose 3	Cohort 4: Dose 4	Cohort 5: Dose 5
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			

subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Myoclonus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Subcapsular renal haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 6: Dose 6	Cohort 7: Dose 7	Cohort 8: Dose 8
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Myoclonus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Subcapsular renal haematoma			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 40 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Large intestinal obstruction			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Subcapsular renal haematoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1: Dose 1	Cohort 1: Dose 1a	Cohort 2: Dose 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	1 / 1 (100.00%)	4 / 5 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Arteriovenous graft site stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Humerus fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Scapula fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Thermal burn			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Duodenitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	2
Rectal haemorrhage			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Polyarthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pustule			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Folate deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypervolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin B12 deficiency			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 3: Dose 3	Cohort 4: Dose 4	Cohort 5: Dose 5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	5 / 6 (83.33%)	2 / 3 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Arteriovenous graft site stenosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Humerus fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Scapula fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Thermal burn			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Duodenitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Skin ulcer			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2

Polyarthritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vaginal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Folate deficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypervolaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 6: Dose 6	Cohort 7: Dose 7	Cohort 8: Dose 8
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	2 / 5 (40.00%)	3 / 6 (50.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arteriovenous graft site stenosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Humerus fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Scapula fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Thermal burn			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Duodenitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Rectal haemorrhage			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle twitching			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Polyarthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Synovial cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vaginal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Folate deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypervolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 40 (67.50%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pain			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Sinus congestion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Arteriovenous graft site stenosis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Humerus fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Scapula fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Thermal burn			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dental caries			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Duodenitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Rectal haemorrhage			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Muscle twitching			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		

Polyarthritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pustule			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Vaginal infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Folate deficiency			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperkalaemia			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hypervolaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vitamin B12 deficiency			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2015	This amendment was implemented to address changes requested by United states food and drug administration (USFDA) Changes to Inclusion criteria - Ferritin: lowered inclusionary values. This criterion was applied in cohort 1 only. Study stopping rule and Cohort stopping rule: 1 or more SAEs that were not clearly related to the patients underlying disease reported Liver safety monitoring: AST/ALT > 3 x ULN or TBL >1.5 x ULN repeat LFT within 48 hours
24 July 2015	This amendment was implemented to address changes requested by USFDA Study stopping rule: Two or more patients experience a severe AE (s) (common terminology criteria (CTC) AE grade 3 that does not qualify as an SAE) during the study. Two or more Hy's law cases Cohort stopping rule: One patient experiences a severe AE (CTC AE grade 3 that does not qualify as an SAE) during the study that is not clearly related to the patient's underlying disease. One Hy's law case
10 November 2015	This amendment was implemented to address changes requested by Medicines and Healthcare products Regulatory Agency (MHRA) during their review Confirmatory language changes for better clarity in study design to include PK data for confirmation and consistency along with removing the duplicate text to clarify that a communication plan on dissemination of safety information to investigators for dose escalation meetings in Part 1 and clarify dose escalation stopping rules Added a statement for better clarity on the management of renal bone disease at site
04 February 2016	The amendment was implemented to address operational issues based on investigator feedback and lower ferritin inclusion criterion Study design: extending the screening period to 60 days and clarification on post-dialysis PK samples collection. Updated the language for treatment assignment, patients domiciliation and emergency breaking of assigned treatment code Changes to Part 1 and Part 2 assessment schedules Updated the inclusion and exclusion criteria.
12 August 2016	The amendment was implemented to increase the ferritin inclusion criterion based on clinical data from the first dosed patients. This criterion was applied in cohorts 2-5. Updated study design figure and patients eligibility criteria.
24 May 2017	The amendment was implemented to conclude Cohort 2 and enable an interim analysis on five rather than six patients. Five patients in Cohort 2 received CSJ137 dose 1 (same dose as in Cohort 1). Clarified prolonged iron response definition. Updated to account for repeat dose design of part 2 for pregnancy and assessments of fertility
25 July 2017	The amendment was implemented in response to the MHRA deficiency letter as a part of an iCTA review. Updated EudraCT number, assessment schedule and a reference Clarified study completion and post-study treatment follow up time as 115 days following last CSJ137 dose Updated exclusion criterion

20 March 2018	The amendment was implemented to summarize available safety data and allow for further dosing, to expand the upper limit of ferritin inclusion criteria and to redefine the mPAD. Updated dose escalation scheme. Updated inclusion criteria. These criteria were applied in cohorts 6-8. Updated intravenous iron management rules
29 March 2018	The amendment was implemented to adapt the protocol design after 10 patients have received CSJ137, to reach a pharmacologically active dose more rapidly without compromising safety. Implemented an adaptive dose escalation strategy in the remaining cohorts in Part 1. Extended the dose escalation from Part 1 to one dose level higher than the minimum PAD Changed the Part 2 design from a three arm single dose to a two arm repeat dose study with a maximum of 1 repeat dose (2 doses in total).
16 April 2019	The amendment was implemented to revise the mPAD based on the emerging data from Cohorts 5 and 6 in Part 1 Updated IV iron supplementation management conditions. Updated blood sampling time-points Revised mPAD definition Minor changes to various sections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: